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Morphine-Induced Modification of Quinine Palatability: Effects of Multiple Morphine–Quinine Trials

SHARON N. D. A. CLARKE AND LINDA A. PARKER[1]

Department of Psychology, Wilfrid Laurier University, Waterloo, Ontario N2L 3C5, Canada

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CLARKE, S. N. D. A. AND L. A. PARKER. *Morphine-induced modification of quinine palatability: Effects of multiple morphine-quinine trials.* PHARMACOL BIOCHEM BEHAV 51(2/3) 505-508, 1995.—Morphine pretreatment attenuates aversive taste reactions elicited by quinine solution when assessed by the taste reactivity test. To determine whether this effect changes across trials, rats were administered morphine (2 mg/kg, subcutaneously) 30 min before a 5-min intraoral infusion of quinine solution (0.05%) on each of eight trials. Neither tolerance nor sensitization developed to morphine-induced attenuation of quinine aversiveness; morphine suppressed quinine-elicited aversive reactions on each trial. In addition, when tested in the absence of morphine, rats displayed a reduced aversion to quinine, suggesting that quinine became conditionally less aversive following previous pairings with morphine.

Morphine Palatability Quinine Taste Taste reactivity Ingestion Reward

MORPHINE enhances eating and drinking, possibly by modifying the palatability of tastants (1–3,6,7,12). Traditionally, investigations of the effect of morphine on tastants have relied on intake measures; yet, intake measures are influenced by a number of factors other than palatability. Recently, however, using the taste reactivity test (4), a direct measure of palatability, it has been demonstrated that morphine modifies the palatability of tastants (2,11). When intraorally infused with 0.5% quinine solution, 30 min after a subcutaneous (SC) injection of morphine (2 mg/kg), rats displayed suppression of aversive taste reactions (11). Hence, morphine appeared to reduce the aversiveness of quinine. This effect was subsequently replicated and extended to a higher quinine concentration (0.1%), and to familiar as well as novel quinine.

The present experiment assessed whether the strength of the effect of morphine on quinine palatability changes over trials. Rats received eight conditioning trials during which the taste reactions elicited by quinine solution were assessed 30 min after an SC injection of morphine or saline. In addition, after trials 3 and 8, taste reactions elicited by quinine alone were measured in a test for the establishment of a conditional palatability shift following pairings with morphine.

METHOD

Subjects

Subjects were 23 experimentally naive, male Sprague–Dawley rats, purchased from Harlan-Sprague Dawley Breeding Laboratories (Indianapolis, IN), weighing 210–260 g at the start of the experiment. They were maintained on ad lib rat chow and water throughout the experiment, and were housed individually in stainless-steel cages. The housing room was illuminated on a 12 L : 12 D schedule.

Procedure

Surgery. One week after arriving in the laboratory, the rats were implanted with intraoral cannulae as previously described by Parker (9). After being deprived of water for 24 h, each rat was anaesthetized with atropine [0.5 mg/kg, intraperitoneally (ip)], followed by ketamine (100 mg/kg, ip) and xylazine (3 mg/kg, ip) 15 min later. A 15-ga, thin-walled, stainless-steel needle was inserted through the rat's skin in the mid-neck region, brought subcutaneously behind its ear along the inside of the cheek, and exited through the soft part of its cheek behind the first molar. The skin around each of the

[1] To whom requests for reprints should be addressed.

punctured sites was swabbed with iodine. With the needle in place, a 10.2-cm length of polyethylene tubing was inserted through the barrel. The needle was then removed, and the tubing was secured at the neck by a 20-ga intramedic adapter, and in the mouth by a 5-mm plastic washer.

Taste reactivity testing. One week after recovering from surgery, the rats were given taste reactivity adaptation trials on each of 3 days. For the adaptation trials, each rat was placed in the glass taste reactivity test chamber (22.5 × 26.0 × 20.0 cm). The room was illuminated by four 100-W lightbulbs with two on either side of the chamber and two aimed at a mirror below the chamber. Once the animal was placed in the chamber, its cannula was connected to an infusion pump (Model 22; Harvard Apparatus, St Laurent, Quebec, Canada) by a 35-cm-long tube. One minute later, the rat received a 5-ml intraoral infusion of water at the rate of 1 ml/min for 5 min.

After three adaptation trials, the rats received taste reactivity conditioning trials. These conditioning trials were identical to the adaptation trials, except that the rats received an injection (1 ml/kg) of 2 mg/ml morphine, SC, (contingent group, $n = 12$) or of saline solution (noncontingent group, $n = 11$), 30 min before receiving a 5-ml intraoral infusion of 0.05% (6.39 × 10^{-4} mol) quinine sulfate solution at the rate of 1 ml/min for 5 min, in the taste reactivity chamber. Immediately before the injection, each rat's food and water were removed and were returned 1 h later. The rats received a total of eight conditioning trials with each trial separated by 72 h. On the days immediately following conditioning trials, all rats received noncontingent trials. On the noncontingent trial, each rat's food and water were again removed immediately before the contingent group of rats received saline injections and the noncontingent group received morphine injections, in the same dosage and concentrations as during conditioning. Thirty minutes later, they were placed in the taste reactivity chamber for 5 min. The rats were treated identically on the noncontingent trials as on the conditioning trials except that they were not infused with quinine solution following the injection.

Three days after the third and eighth conditioning trials, the rats received a test trial. During each of these test trials, all of the rats were injected with saline (1 ml/kg, SC), 30 min before a 5-min infusion of quinine. Food and water were removed and returned as during the conditioning trials.

During each conditioning trial and test trial, the orofacial and somatic responses of each subject were recorded on videotape, with a camera that focused on a mirror beneath the

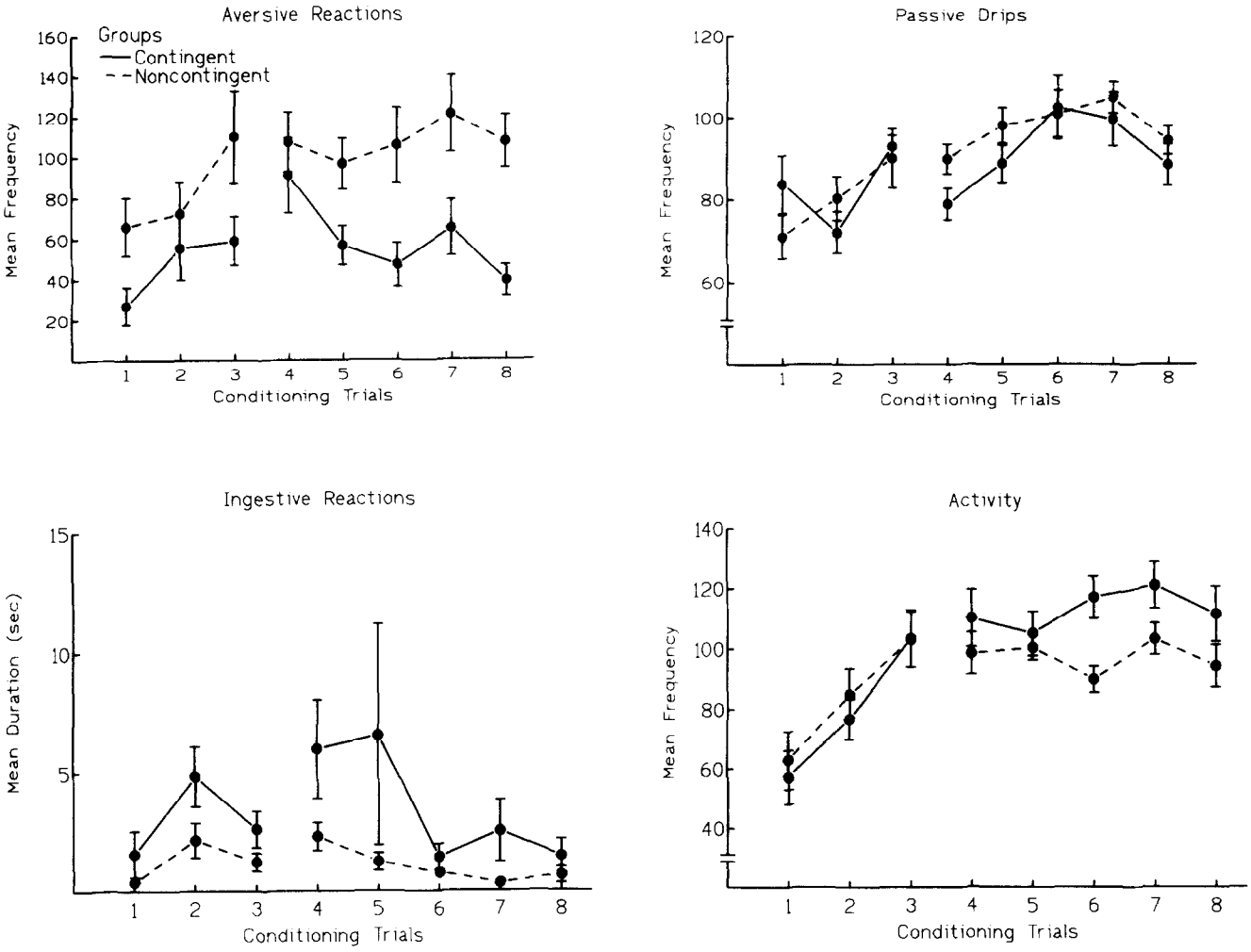

FIG. 1. The mean frequency or duration (seconds) of aversive reactions, passive drips, ingestive reactions, and activity displayed during the 5-min intraoral infusion of quinine solution on conditioning trials.

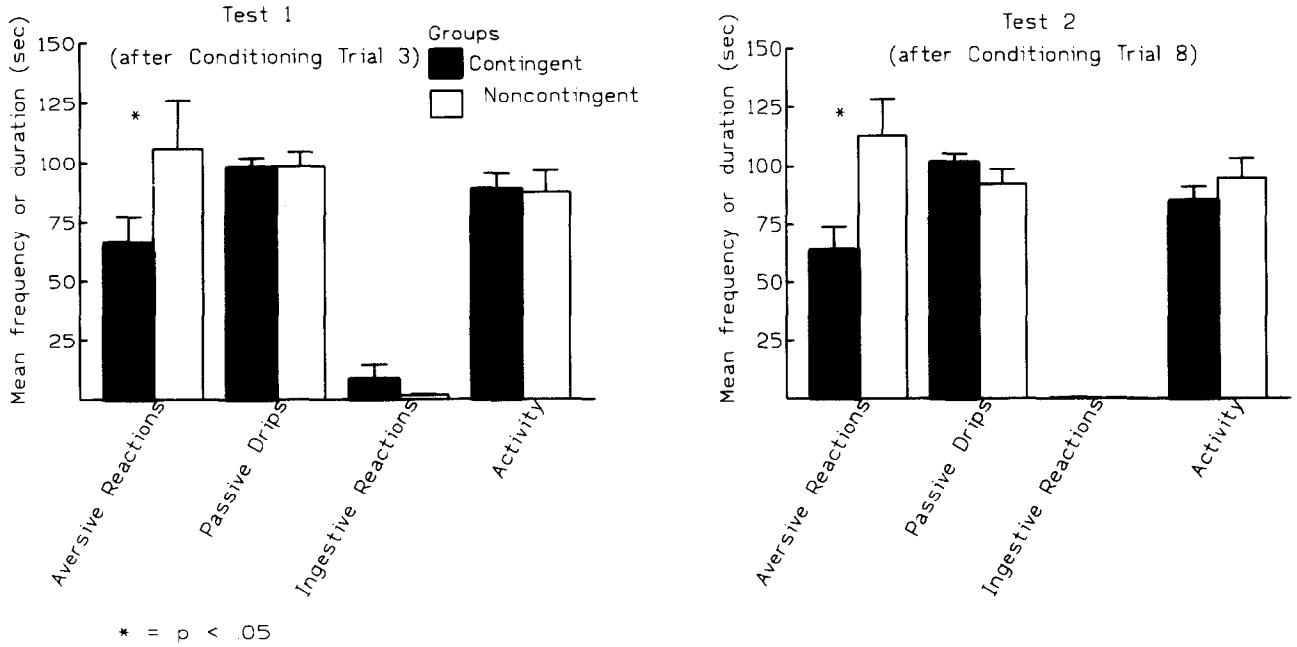

FIG. 2. The mean frequency or duration (seconds) of aversive reactions, passive drips, ingestive reactions, and activity displayed during the 5-min intraoral infusion of quinine solution on test trials.

chamber that was hung at an angle to facilitate viewing of the rat's ventral surface.

Scoring of Behavioral Categories

The videotapes of the taste reactivity test were scored in real time using the event recorder program, "The Observer" (Noldus, Inc., Wageningen, the Netherlands) for an IBM computer by a rater who was unaware of the experimental conditions. This method has been demonstrated to be reliable (10). Four behavioral categories were assessed: aversive reactions, neutral or mildly aversive reactions, ingestive reactions, and activity. Aversive reactions included the combined frequency of five taste reactions: chin rubbing (forward projection of the head with the chin rubbing against a substrate), gaping (triangular, wide opening of the mouth), paw treading (rhythmic pushing of the forepaws against the floor of the cage), limb-flicking (rapid shaking of the forelimbs), and head shakes. The behavioral category of neutral and mildly aversive reactions consisted only of the frequency of passive drips (number of drops of the test solution that dripped from the rat's mouth to the floor when the rat was not actively ejecting the solution by an aversive response). Ingestive reactions represented the duration (seconds) of the display of three ingestive reactions: tongue protrusions (extension of the tongue), mouth movements (movements of the mouth without extensions of the tongue), and paw licks. Finally, the behavioral category of activity represented the frequency of rearing (occurences of vertical movements with both forelimbs off the floor of the chamber) and active locomotion (occurences of horizontal movements along the floor of the chamber with both forepaws on the floor) throughout the infusion period.

RESULTS

Conditioning Trials

Figure 1 presents the mean frequency or duration of aversive reactions, passive drips, ingestive reactions, and activity across conditioning trials for the contingent and noncontingent groups. Separate 2 × 8 (Group × Conditioning Trials) mixed-factor analyses of variance (ANOVAs) revealed a significant Group effect for aversive reactions [$F(1, 21) = 15.81$, $p < 0.01$] and for ingestive reactions [$F(1, 21) = 7.9$, $p < 0.05$]. The contingent group displayed fewer aversive reactions and spent more time exhibiting ingestive reactions than did the noncontingent group across the conditioning trials. However, the groups did not differ on the basis of the frequency of passive drips and activity elicited by the quinine solution. Notably, the mixed-factor ANOVAs did not reveal a significant Group × Trials interaction for any of the assessed behaviours; therefore, there was neither evidence for the establishment of tolerance nor sensitization across trials.

Test Trials

Figure 2 presents the mean frequency or duration of aversive reactions, passive drips, ingestive reactions, and activity elicited by quinine solution by the contingent and noncontingent groups during each test trial. Test 1 was conducted after three conditioning trials, and Test 2 was conducted following eight conditioning trials. The contingent group displayed significantly fewer aversive taste reactions during the quinine infusion than the noncontingent group during Test 1 [$t(21) = 1.8$, $p < 0.05$] and during Test 2 [$t(21) = 2.7$, $p < 0.01$]. The groups did not differ in the mean frequency or duration of any of the other behaviours on either test.

DISCUSSION

Repeated pairings of morphine and quinine did not modify the ability of morphine to attenuate the aversive taste properties of quinine. Because this effect was neither diminished nor enhanced across eight conditioning trials, neither tolerance nor sensitization was established to the modification of quinine palatability by morphine.

The results of this experiment also provide evidence that

quinine became conditionally less aversive as a result of the contingent morphine–quinine pairings. During the conditioning trials, the contingent group displayed suppressed aversive reactions to quinine in comparison to the noncontingent group. After only three conditioning trials, the contingent group displayed similar suppressed aversive reactions to quinine, in the absence of morphine pretreatment. This observation suggests that the effects of morphine became associated with the quinine conditioned stimulus, resulting in suppressed aversive reactions or drug-similar conditioned responses.

The conditioned suppression of aversive taste reactions elicited by quinine solution during the test trials suggests that morphine conditionally shifted the palatability of quinine; however, the shift was not from an aversion to a preference, because the shift was not evident by the measure of ingestive reactions. Morphine-conditioned taste preferences have been reported using consummatory tests with extremely low doses of morphine (5,8) and employing a simultaneous rather than trace conditioning procedure (5).

The present finding suggests that conditioned attenuation of quinine aversion can be established after three pairings with a higher dose of morphine (2 mg/kg, SC), 30 min before an intraoral infusion of quinine solution. Unpublished results in our laboratory indicate that such an effect is not established when the same dose of morphine repeatedly follows the quinine infusion during conditioning trials. Therefore, the temporal relationship between the taste and the effect of a reinforcing drug may be crucial to the establishment of conditioned palatability shifts. The establishment of a conditioned increase in the palatability of a tastant may be facilitated when the taste paired with morphine is naturally aversive. The taste reactivity test therefore provides a highly effective method of assessing conditioned enhancement of palatability by pairings of aversive tastants with rewarding drugs.

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